REMARKS

Claims 1-3, 5, 8-22, 24-45, 47-68, 70, 126 and 127 are currently pending. Claims 18-22, 24-45, 47-68 and 70 were withdrawn from consideration. Claims 1 and 2 are amended herein solely to clarify the claim language, and are submitted without prejudice and without acquiescence. Applicants reserve the right to pursue the original claim material in subsequent prosecution. New claim 128 is presented herein, and support for the claim is in the specification in numerous places, such as in the Abstract. No new matter is entered herein.

Issues Under 35 U.S.C. §102(b)

Claims 1-3, 5, 8, 9, 13-16, 126 and 127 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Delmotte *et al.* (U.S. Patent No. 5,989,215; hereinafter referred to as "Delmotte"). Applicants respectfully disagree.

Delmotte concerns a medical device for delivery of biochemically reactive liquids, such as fibrin resulting from the mixture of first and second biochemical solutions comprising fibrinogen and thrombin/calcium, respectively. As detailed in column 3, lines 31-61, Delmotte teaches delivery of fibrin to a surface comprising providing a liquid solution of fibrinogen; providing a liquid solution of thrombin; providing an aerosolization unit; spraying fibrinogen onto a surface; spraying thrombin separately from fibrinogen onto the surface; and mixing the fibrinogen with the thrombin on the surface to make fibrin.

The biological mechanism of fibrin formation is known in the art, such as, for example, described in U.S. Patent No. 6,262,236, col. 1, lines 28-44:

> The formation of crosslinked fibrin II polymer proceeds by the fibrinogen being converted by thrombin to fibrin I monomer, which spontaneously polymerizes to form fibrin I polymer....The fibrin I polymer is then converted by thrombin to fibrin II polymer.... The fibrin II polymer, under the influence of factor XIIIa--known as activated factor XIII--is then crosslinked to form crosslinked fibrin II, which is the fibrin clot. Factor XIII is activated by thrombin in the presence of calcium ions. (emphasis added)

In Delmotte, there is administration of monomeric fibrinogen protein and a thrombin protein/calcium mixture. There is no teaching in Delmotte that the first and second biochemical solutions are each of a particular nature, and certainly not a ***polymer*** composition and a ***cross-linking*** composition. In fact, wherein fibrinogen and thrombin are separated until the formation of fibrin can occur in a desired manner, ***neither*** the fibrinogen solution

nor the thrombin/calcium solution comprises a polymer. Thus, although Delmotte teaches separate containers for two solutions for the purpose of avoiding polymerization, it does not teach separate containers for administering a ***polymer*** and a ***cross-linking*** composition. In summary, Applicants administer a polymer and then cross-link it, whereas Delmotte administers a monomer, cleaves it, and then cross-links it to form the polymer.

Thus, Delmotte does not teach all of the elements of Claim 1 and, therefore, its dependents, and Applicants respectfully request removal of this rejection.

Furthermore, in particular Delmotte does not teach the additional claim elements differentiated in claims 13-15, which address a cross-linker comprising a salt of a divalent cation. Fibrin is cross-linked by Factor XIII following the activation of Factor XIII by thrombin in the presence of calcium, and therefore Delmotte clearly at the very least does not teach these particular claims.

Issues Under 35 U.S.C. §103(a)

Claims 1-3, 8-11, 13-17, 126, and 127 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,945,100 (hereinafter referred to as "Fick"). Applicants respectfully disagree.

Fick teaches delivery of therapeutic agents into solid tumors by employing methods and compositions to enhance the amount of material delivered into a tumor. In particular, polymeric materials that gel or solidify at the time of or shortly after implantation are utilized to deliver therapeutic agents, such as gene therapy compositions, and the delivery preferably comprises a catheter. Given that the presence of a cross-linker initiates and leads to cascading of the polymerization process, the Examiner contends that it would be obvious for the cross-linker and polymer composition to be administered separately from separate containers/compartments. Applicants' invention is not obvious in view of Fick, given that this presumably important parameter is never mentioned or suggested in Fick, and a skilled artisan would not be motivated to utilize it.

The Examiner does not point to anywhere in Fick that suggests implicitly or that states explicitly that there is motivation to keep the compositions separate. Where applicable, the findings ***should clearly articulate which portions of the reference support any rejection***. Explicit findings on motivation or suggestion to select the claimed invention should.....be

articulated in order to support a 35 U.S.C. 103 ground of rejection. *In re Dillon*, 919 F.2d at 693, 16 USPQ2d at 1901; *In re Mills*, 916 F.2d 680,683, 16 USPQ2d 1430,1433 (Fed. Cir. 1990). Obviousness can not be based on "common knowledge and common sense of a person of ordinary skill in the art without any ***specific hint or suggestion in a particular reference***." *In re Lee* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) (emphasis added). Given that Fick does not suggest or teach separation of the compositions, Applicants respectfully assert that the Examiner is inferring this parameter from the claimed invention, which is inappropriate. The reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

In fact, given the lack of teaching or suggestion regarding separate administration of the polymer/cross-linker in Fick, the two components therein may be mixed at a temporal and/or physical distance from the localized region in a patient and subsequently applied by catheter to the region. Applicants overcome such problems that would manifest with Fick absent a teaching, suggestion or motivation to keep the compositions separate by providing a solution to prevent pre-mixing issues such that solidification does not occur at the time of injection. Applicants' invention ensures that solidification occurs after the components have been injected by using different administration parameters, including administration more or less simultaneously from separate containers. The configuration in Fick does not guarantee that polymerization occurs afterward, and it is deleterious for polymerization to occur during the administration, such as within a syringe. ***This problem is not recognized in Fick, so there would be no motivation to overcome it.*** In the specific embodiments of the present claims, Applicants devised a way to avoid this issue by injection from two separate containers wherein mixing occurs in the localized region, such as in the tumor.

Of particular relevance in the present matter, courts have long held that to render a claimed invention obvious, the prior art must recognize the source or existence of the problem in the first place. For example, the U.S. Supreme Court has held that in the case of a known problem, the identification of the source of that problem is patentable, even where the solution is obvious once the source is known. *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 68 (1923). Similarly, a "patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." *In re Sponnoble*, 160 U.S.P.Q. 237, 243 (C.C.P.A. 1969). A

corollary to these principles is where the prior art fails to recognize the existence of a problem in the first place. In this regard, the CCPA has held that it is improper to conclude that an invention is obvious absent evidence that one of skill would have recognized that an underlying problem existed. *In re Nomiya*, 184 U.S.P.Q. 607 (CCPA 1975).

As noted in passing above, the caselaw strongly supports a conclusion of non-obviousness in the present case. The Supreme Court, in *Eibel Process*, noted that the discovery of the source of a known problem is strong evidence of non-obviousness:

> ... we must not lose sight of the fact that one essential part of Eibel's discovery was that the trouble causing the defective paper product under high machine speed was in the disturbance and ripples some ten feet from the discharge and that they were due to the unequal speeds of stock and wire at that point and could be remedied by equalizing the speeds. The invention was not the mere use of a high or substantial pitch to remedy a known source of trouble. ***It was the discovery of the source not before known and the application of the remedy for which Eibel was entitled to be rewarded in his patent.***

Eibel, 261 U.S. at 67-68. (emphasis supplied). See also Sponnoble, 160 U.S.P.Q. at 243 ("It should not be necessary for this court to point out that a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.").

Perhaps most relevant to our situation is the Nomiya case, where the CCPA, relying on the principles of *Eibel Process* and *Sponnoble*, held that invention is found in the recognition of a previously unknown problem:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, ***it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the prior art device, would have been obvious to that hypothetical person of ordinary skill in the art.*** This significance of evidence that a problem was know in the prior art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by [Eibel Process], where the rippling in paper produced on Fourdrinier paper-making machines was known, but the source of the problem was not.

Nomiya, 184 U.S.P.Q. at 612-13. (emphasis added)

In the present case, as in *Nomiya*, the Action fails to present substantial evidence that those of skill recognized the existence or source of the problem associated with the mixing of the two solutions.

As stated, there is no motivation for separate containers because Fick does not imply or state that it would be preferable that they should be kept separate. Fick teaches a catheter for administration of the composition and makes no suggestion or indication that it should be bi-compartmental, for example. Furthermore, when the solidification can occur shortly after injection (Abstract; col. 4, lines 52-55), there would be no motivation to keep the compositions separate. Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor. *Para-Ordnance Manufacturing, Inc. v. SGS Importers International, Inc.* 73 F.3d 1085, 37 USPQ2d 1237 (Fed. Cir. 1995), *cert. denied*, 519 U.S. 822 (1996). To establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). There must be a teaching or suggestion to make the claimed limitations, and Applicants remind the Examiner that the level of skill in the art cannot be relied upon for suggestion. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Thus, Applicants assert that the Office has not established a *prima facie* case of obviousness to reject the claims under 35 U.S.C. §103. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, (Fed. Cir. 1991).

Finally, even if Fick had suggested that the compositions should be administered separately, there is no suggestion that the administration should be from separate containers, as delineated in Applicants' claim 1. The administration could be from the same containers at separate times, such as successive administration of one after the other through the catheter.

Thus, Applicants state that the claimed invention is not obvious and respectfully request removal of this rejection. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. AH-UTXC:681US from which the undersigned is authorized to draw.

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Respectfully submitted,

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